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ORIGINAL ARTICLE

Surgery is essential in squamous cell cancer of the rectum

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Abstract
Purpose Squamous cell cancer (SCC) is a rare histological subtype of rectal cancer. It is unclear whether SCC should be treated by multimodal therapy, including surgery, or by chemoradiation alone. The objective of the study was to define an optimal treatment strategy.
Methods Patients with rectal cancer and SCC histology were identified in the Surveillance Epidemiology and End Results Database between 1990 and 2013. According to treatment, three groups were defined: radiotherapy and surgery (RT/SX), radiotherapy (RT), and surgery (SX). Overall survival (OS) and disease-specific survival (DSS) for localized, regional, and distant disease were assessed using a multivariable Cox regression model.
Results Out of 856,435 colorectal cancer patients, 1747 with SCC of the rectum were eligible. Four hundred and fifty-five were treated with RT/SX, 994 with RT, and 298 with SX. Adjusted hazard ratios (HR) did not differ for OS and DSS in localized disease. In regional disease, OS and DSS were improved for RT/SX compared to RT (HR 0.751, 95% CI 0.566–0.997, $P = 0.048$ and HR 0.679, 95% CI 0.478–0.966, $P = 0.031$). In distant disease, OS and DSS were not different.
Conclusions Multimodal therapy including surgery improved OS and DSS compared to receiving a treatment without surgery for regional disease in rectal SCC. No difference was observed in localized and distant disease. The findings contradict with recent reports favoring definitive chemoradiation.

Keywords Rectal cancer · Squamous cell cancer · Multimodal treatment · Survival

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Introduction

The vast majority of rectal cancers are adenocarcinomas and are best treated by total mesorectal excision with or without neoadjuvant chemoradiation depending on staging and localization [1]. However, a minority of 0.25 to 1.0% of all rectal cancers are squamous cell carcinomas (SCCs) [2, 3]. SCC is the typical histology of anal cancer. In anal cancer surgery in the form of abdominoperineal excision (APE) was the cornerstone of treatment until the 1980ies. Yet, it was associated with a high local failure rate. Today, combined therapy including chemotherapy with 5-FU and mitomycin or cisplatin and radiotherapy is the treatment of choice. It has been demonstrated that anal cancer is highly radiosensitive, especially when radiosensitising chemotherapy is added [4]. Surgical treatment is restricted to the local excision for small tumors of the anal margin and APE as salvage treatment in case of failure of prior chemoradiation [5–7].

The underlying etiology of SCC of the colon and rectum remains inscrutable. The most prevalent hypothesis is that squamous metaplasia arises due to chronic stress with subsequent progression to carcinoma. Chronic inflammation may be induced by ulcerative colitis, Crohn's disease, radiotherapy, and infection [8–15].

To date, it remains unclear whether SCC of the rectum should be treated like an adenocarcinoma of the rectum or rather like a SCC of the anal canal [16]. In clinical guidelines,

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no distinct recommendations for this subset of rectal cancer are given [17]. A shift from surgery towards definitive radiotherapy has been observed in the last decade [8].

Using the Surveillance, Epidemiology, and End Results Program (SEER) of the National Institute of Health, this study aimed at comparing survival for different treatment regimens in squamous cancer of the rectum. The objective of the present population-based analysis was to define an optimal treatment strategy for this rare cancer type.

Methods

SEER database

The SEER program is a National Cancer Institute-based authoritative source of cancer data in the USA. Its survival and case listing sessions cover approximately 27.8% of the US population [18]. SEER receives mortality data from the National Center for Health Statistics and population data periodically from the Census Bureau. The population-based center registries of SEER program include Alaska Native Tumor Registry, Los Angeles, San Francisco-Oakland, San Jose-Monterey, Greater California, Connecticut, Detroit, Atlanta, Rural Georgia, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound, Greater Georgia, and Utah.

Selection of cases

Data search was limited to the time period 1990–2013 and for the location "rectum and rectosigmoid." In patients with SCC, the histology subtypes according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3/WHO 2008) 8070/3 to 8074/3 were attributed.

Survival according to entity

The 5-year overall survival (OS) and disease-specific survival (DSS) of patients with squamous cell rectal cancer, adenocarcinoma of the rectum, and with anal cancer (SCC of the localization "anal, anal canal, and anorectum") are compared. The survival data are computed by the SEER*Stat software using the survival session tool. In OS, any death was considered an event whereas in DSS, only death from the specific cancer was considered.

Survival according to treatment

In rectal SCC, the OS and DSS survival stratified according to the received treatments was investigated. For this analysis, patients with a location site different than "rectum" or "rectosigmoid," with missing histological proof of diagnosis, with undefined treatment, with unknown staging, and patients that did not receive radiotherapy or surgery or had undefined treatment were excluded. Subgroup analysis was performed for localized disease, regional disease, and distant disease.

Survival analysis according to treatment was performed using the SEER*Stat case listing tool. The included patients differ in the SEER*Stat case listings and the SEER*Stat survival analysis. Patients were allocated to the following three groups according to received therapy: combined treatment of radiotherapy and surgery (RT/SX), radiotherapy alone (RT), and surgery alone (SX) (Fig. 1). Age, sex, ethnicity, tumor stage (localized, regional, or distant disease; according to the SEER Staging Manual 2000), T-stage, N-stage, M-stage, UICC stage, and the median follow-up time are listed for the three groups.

The OS and DSS for the three treatment groups were adjusted for sex and age and were expressed in a Cox-regression model separately for localized, regional, and distant disease. The differences of the hazard ratio (HR) in OS and DSS between different treatments were tested for significance.

To detect changes in treatments offered over time, the proportion of patients being treated by RT/SX, RT, and SX was calculated for the time periods 1990–2000 and 2001–2013 and compared.

Statistical analysis

SEER*Stat software (version 8.3.2, National Cancer Institute) provided by the SEER program was used to select included cases and perform survival analysis. Furthermore, the software was used to compare the characteristics and survival in rectal adenocarcinoma, anal cancer, and squamous cell rectal cancer. Five-year OS and DSS and the corresponding standard error (SE) are expressed as listed by SEER*Stat.

Case listings were obtained, grouped, and stored in a Microsoft Excel (version 14.4.5 Microsoft Inc., WA) database. The data was analyzed using SPSS software (SPSS 17, IBM, Chicago, IL).

Continuous data were expressed as the mean ± standard deviation (SD) or 95% confidence intervals (CI). Statistical significance was tested using Student's t test with two-tailed P values. For comparison of categorical variables, chi-squared test was used. In a Cox regression model, survival curves for OS and DSS were adjusted for age and sex. Of adjusted survival, estimated hazard ratios were obtained to compare different treatments pairwise. The level of significance was defined as $P \leq 0.05$.

Results

Baseline characteristics

In the study period 856,435 patients were diagnosed with colorectal cancer. Of those 2771 had SCC of the colon or

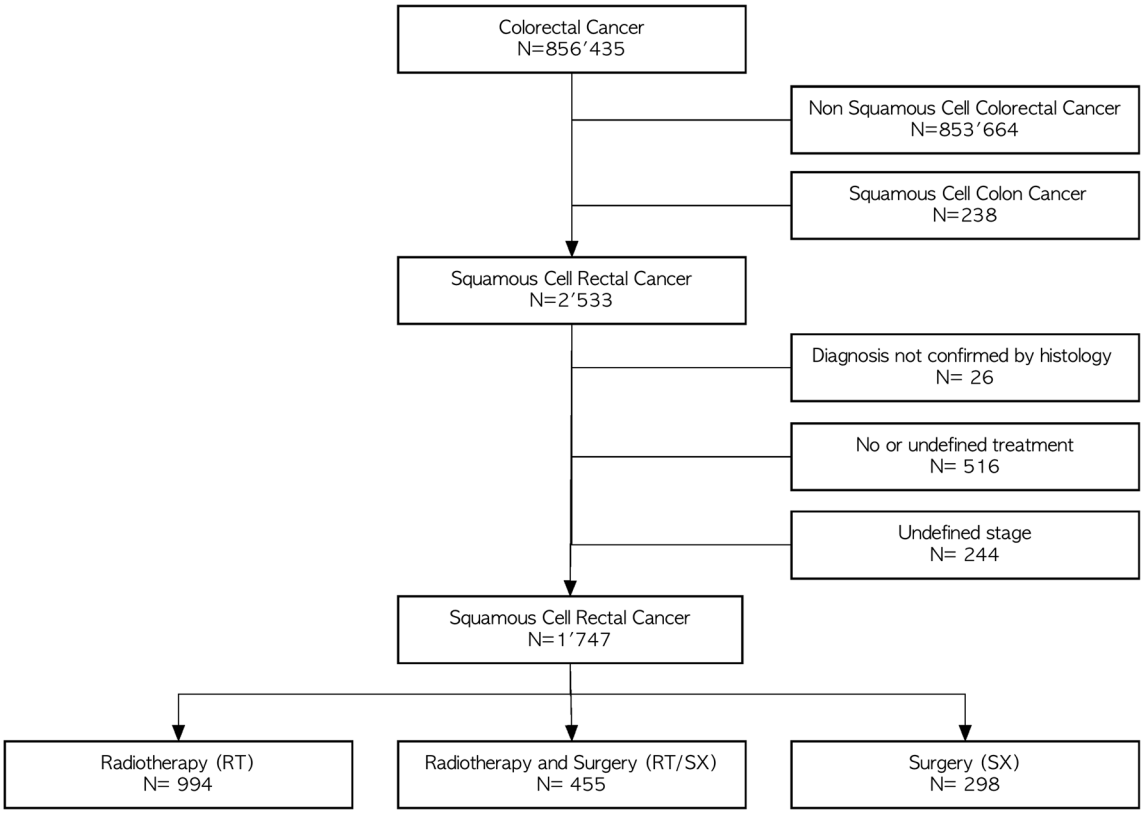

Fig. 1 Flowchart depicting included and excluded patients

rectum (0.3%). Of the 199,858 patients with cancer of the rectum or rectosigmoid, 2533 (1.3%) had SCC. After exclusion of cases with missing histological proof of diagnosis, with undefined treatment, and with unknown staging, 1747 patients were available for further analysis. According to the received treatment algorithms, three groups were defined: 455 (26.0%) were treated with RT/SX, 994 (56.9%) with RT, and 298 (17.1%) with SX alone (Fig. 1). Patients in the three treatment groups differed in age, sex, ethnicity, stage (local, regional, distant), T-stage, N-stage, and UICC-stage (Table 1). The median follow-up time overall and for RT/SX, RT, and SX were 3.0 (0–23.7), 3.5 (0–23.7), 2.8 (0–21.3), and 2.9 (0–23.1) years, respectively.

Survival according to entity

Based on the SEER*Stat survival session analysis, there were 165,057 patients with adenocarcinoma of the rectum and rectosigmoid (ACR); 18,518 patients with cancer of the anus, anal canal, and anorectum (CA); and 2001 patients with SCC of the rectum and rectosigmoid. The actual 5-year OS of ACR was 56.4%, of CA 59.3%, and for rectal SCC 53.3% ($P < 0.001$). The 5-year DSS was 65.2, 70.2, and 62.7% for ACR, CA, and rectal SCC, respectively ($P < 0.001$).

Survival according to treatment in rectal SCC

Survival curves adjusted for age and sex expressed for localized, regional, and distant disease are shown for OS in Fig. 2 and for DSS in Fig. 3.

Adjusted HR for OS and DSS are shown in Table 2 for a localized, regional, and distant disease. In adjusted analysis there was no difference in OS and DSS for localized disease. However, OS and DSS was improved for RT/SX compared to RT (HR 0.751, 95% CI 0.566–0.997, $P = 0.048$; and HR 0.679, 95% CI 0.478–0.966, $P = 0.031$). No difference in OS and DSS was observed in distant disease irrespective of the treatment regime.

The proportions of patients treated with RT/SX, RT, and SX for the time period 1990–2000 were 30.6, 46.7, and 22.7% and for 2001–2013 24.8, 59.5, and 15.6%. The proportion of patients treated by RT alone increased after the year 2000 ($P < 0.001$).

Discussion

This population-based cohort study revealed an almost 25% improved OS, and more than 30% improved DSS in lymph node positive patients that received multimodal therapy including surgery compared to RT without surgery for rectal

Table 1 Patient characteristics for the treatment groups for rectal squamous cell cancer: radiotherapy alone (RT), combined radiotherapy and surgery (RT/SX), and surgery alone (SX)

Characteristic	RT (n = 994)	RT/SX (n = 455)	SX (n = 298)	P
Age, mean ± SD years	61.6 ± 13.0	58.8 ± 12.5	65.0 ± 15.4	< 0.0001
Gender, n (%)				
Male	297 (29.9)	149 (32.8)	120 (40.3)	0.003
Female	697 (70.1)	306 (67.2)	178 (59.7)	
Ethnicity, n (%)				
Caucasian	860 (86.5)	394 (86.6)	240 (80.5)	0.017
African-American	111 (11.2)	55 (12.1)	44 (14.8)	
Other/unknown	23 (2.3)	6 (1.3)	14 (4.7)	
Stage, n (%)				
Localized	551 (55.4)	229 (50.4)	171 (57.4)	0.251
Regional	319 (32.1)	171 (37.4)	93 (31.2)	
Distant	124 (12.5)	55 (12.1)	34 (11.4)	
UICC stage, n (%)				
Stage I	370 (37.2)	187 (41.2)	127 (42.6)	< 0.0001
Stage II	250 (25.2)	97 (21.1)	77 (25.8)	
Stage III	134 (13.5)	97 (21.4)	46 (15.4)	
Stage IV	119 (12.0)	51 (11.2)	32 (10.7)	
Not available	121 (12.2)	23 (5.1)	16 (5.4)	
T-stage, n (%)				
Tis	55 (5.5)	26 (5.7)	16 (5.4)	< 0.0001
T1	237 (23.8)	140 (30.8)	80 (26.8)	
T2	123 (12.4)	51 (11.0)	46 (15.4)	
T3	256 (25.8)	122 (26.9)	85 (28.5)	
T4	131 (13.2)	70 (15.4)	43 (14.4)	
Tx	192 (19.3)	46 (10.1)	28 (9.4)	
N-stage, n (%)				
N0	578 (58.1)	289 (63.4)	207 (69.5)	< 0.0001
N1	130 (13.1)	93 (20.5)	39 (13.1)	
N2	31 (3.1)	20 (4.4)	18 (6.0)	
N3	6 (0.6)	4 (0.9)	1 (0.3)	
Nx	249 (25.1)	49 (10.8)	33 (11.1)	
M-stage, n (%)				
M0	857 (86.2)	394 (86.6)	256 (85.9)	0.577
M1	119 (12.0)	51 (11.2)	32 (10.7)	
Mx	18 (1.8)	10 (2.2)	10 (3.4)	

SD standard deviation

SCC at a median follow-up of 3 years. However, no difference in OS and DSS was found for localized disease.

Different treatment strategies for rectal SCC are adopted according to SEER. Within the last three decades, the proportion of patients treated by RT without involvement of surgery increased to 59.5% after the year 2000. In a previous systematic review including 142 patients with rectal SCC, an OS of 48% was found for surgery alone and of 86% for definitive chemoradiation including salvage surgery in 44% of cases [8]. From this data, it seems obvious that chemoradiation does improve the prognosis of rectal SCC with the benefit of an increased probability of sphincter preservation. In anal cancer, definitive chemoradiation has largely replaced surgery as the cornerstone of treatment. The introduction of radiotherapy combined with, mostly, 5-fluorouracil and mitomycin has dramatically improved survival compared to abdominoperineal resection [5, 19]. Based on the promising results in anal cancer, several recent small case series have proposed definitive chemoradiation using analogue treatment regimes for rectal SCC as well [12, 16, 20–24]. The mean pathologic complete response in these reports was 57%, and the mean overall survival was 86% with a follow-up between 1 and 192 months [8]. However, response rates in anal cancer are notably higher ranging between 80 and 90% [4, 25, 26]. In the light of the results of the current study showing survival benefits for RT/SX, it is questionable if surgery might be omitted from a multimodal treatment. Especially in locally advanced tumors, failure to chemoradiation is likely more prevalent and

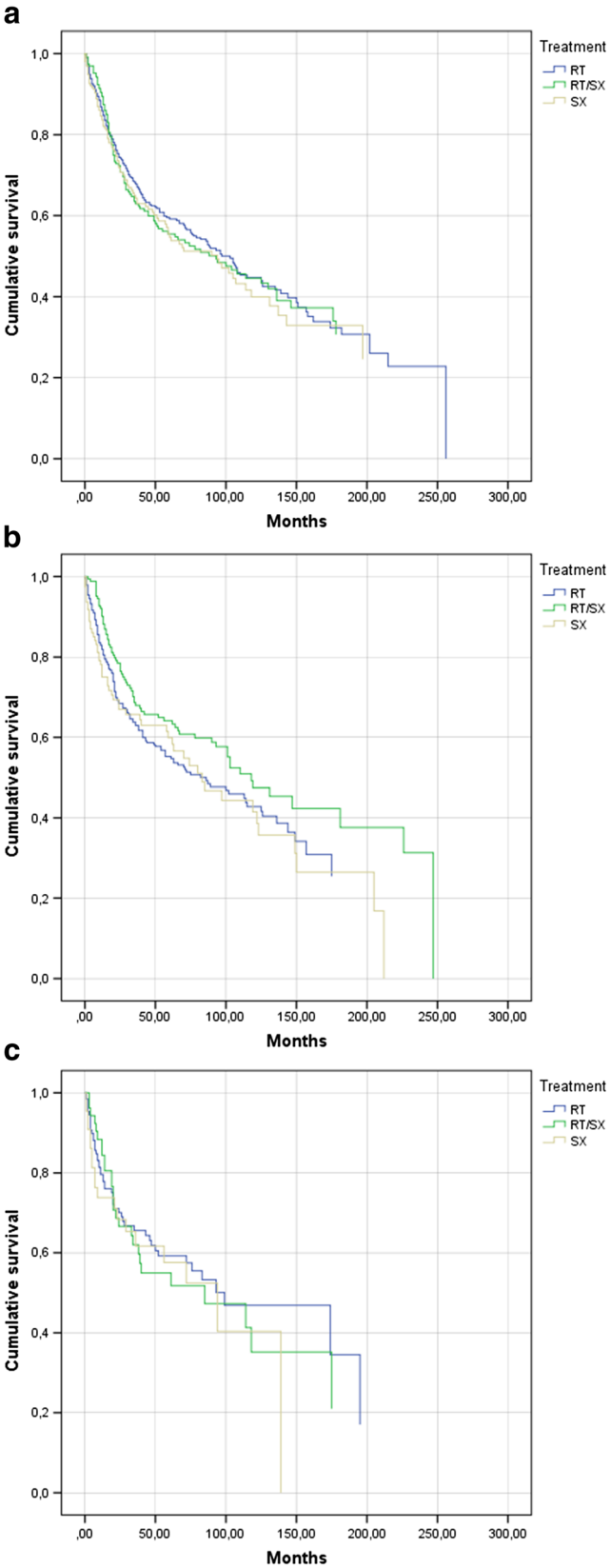

Fig. 2 Cox regression model of overall survival for radiotherapy alone (RT), combined radiotherapy and surgery (RT/SX), and surgery alone (SX) for localized (**a**), regional (**b**), and distant disease (**c**) adjusted for age and sex

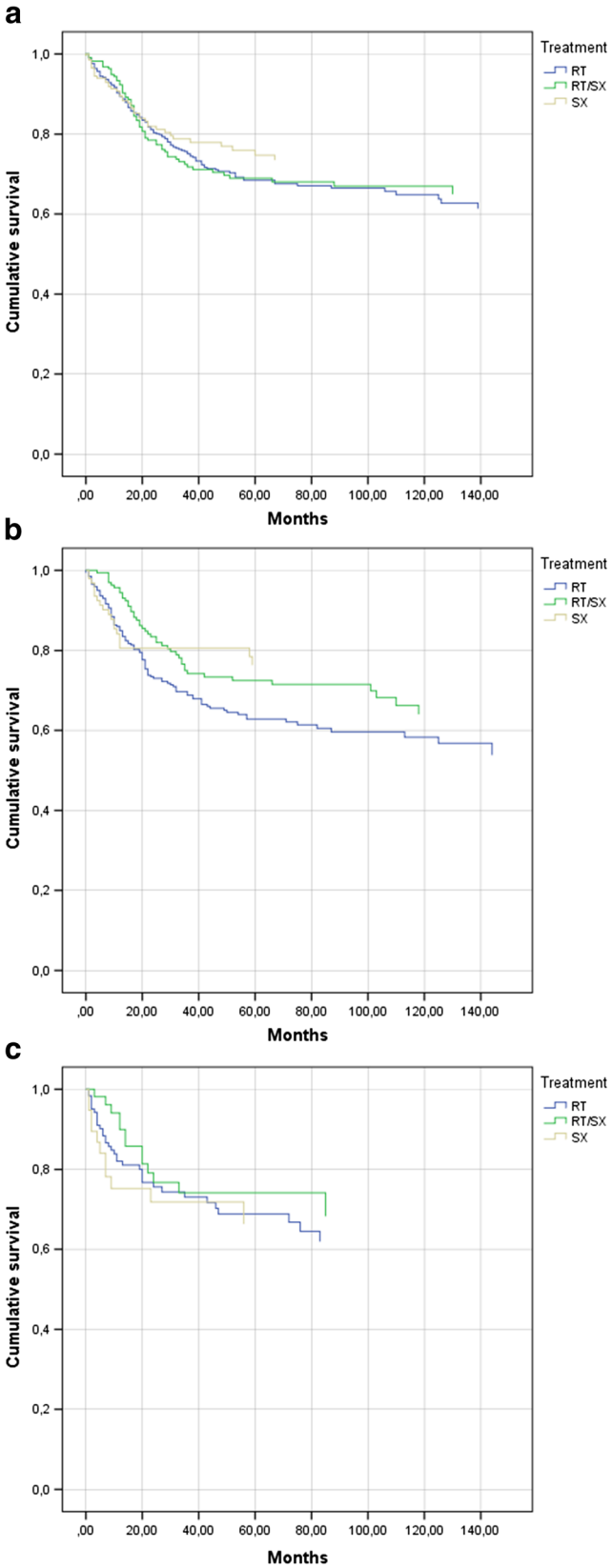

Fig. 3 Cox regression model of disease-specific survival for radiotherapy alone (RT), combined radiotherapy and surgery (RT/SX), and surgery alone (SX) for localized (**a**), regional (**b**), and distant disease (**c**) adjusted for age and sex

Table 2 Hazard ratios (HR) adjusted for age, sex and stage for overall survival (OS), and disease-specific survival (DSS) with 95% confidence interval (CI)

	OS HR	95% CI	*P*	DSS HR	95% CI	*P*
Localized disease						
RT (ref.)	1.0			1.0		
RT/SX	1.007	0.799–1.270	0.951	0.967	0.714–1.311	0.831
SX	1.044	0.928–1.176	0.472	0.888	0.745–1.059	0.186
Regional disease						
RT (ref.)	1.0			1.0		
RT/SX	0.751	0.566–0.997	0.048	0.679	0.478–0.966	0.031
SX	1.030	0.878–1.209	0.715	0.777	0.608–0.994	0.044
Distant disease						
RT (ref.)	1.0			1.0		
RT/SX	1.176	0.730–1.895	0.505	0.775	0.407–1.477	0.439
SX	1.104	0.836–1.459	0.485	1.021	0.718–1.454	0.906

Radiotherapy (RT) is the reference treatment compared to combined radiotherapy and surgery (RT/SX) and to surgery alone (SX)

therefore surgery should eventually not be omitted as part of the therapy.

Although for localized disease no survival benefit was detected for RX/SX compared to RT, however, it is difficult to reliably identify patients that are nodal-negative before treatment. The sensitivity of preoperative detection of lymph node metastasis is as low as 33–58% [27–29]. Therefore, it seems reasonable that RX and SX should preferably be combined. Nevertheless, the potential survival benefits of added surgery must be counterbalanced against the morbidity of rectal resection—in low rectal cancer abdominoperineal resection—including temporary or definite stoma and associated impairment of the quality of life. The decision on the individual treatment plan must be based on the preoperative staging, age and comorbidities of the patient. Furthermore, true rectal SCC has to be meticulously distinguished from anal SCC by ruling out anal involvement as the treatment differs according to the findings of the current study.

A reason for the findings of this study might be that primary SCC of the rectum is a distinct entity that differs significantly from adenocarcinoma of the rectum and squamous anal cancer. In this population-based study, primary SCC accounts for 0.3% of colorectal and more specifically for 1.3% of rectal cancer, which confers to the current literature [2, 3]. With a mean age of 63 years at diagnosis, rectal SCC patients are almost 10 years younger than those with a rectal adenocarcinoma but 5 years older than those with anal cancer [2, 30]. The 5-year DSS is worst in rectal SCC with 62.7%, compared to 65.2% for rectal adenocarcinoma and 70.2% in squamous anal cancer. Rectal SCC does not seem to behave similar as rectal adenocarcinoma nor as squamous anal cancer.

A further difficulty in the non-operative management of rectal SCC is the determination of a complete response. In anal cancer, response to chemoradiation is assessed by digital rectal examination and by pelvic magnetic resonance imaging, computed tomography (CT), or positron emission tomography (PET)-CT [5]. Primary SCC is often not reachable by digital rectal examination; in rectoscopy, it is difficult to assess the response due to present edema and fibrosis. In the most recent reports on non-operative management of rectal SCC, response was evaluated either by digital examination, rectoscopy, and CT [24], by measuring SCC anti-gene and colonoscopy with biopsies [31], or by digital examination, transrectal ultrasound, and CT performed between 6 weeks and 6 months after the end of chemoradiation. It has been shown that primary and metastatic rectal SCC are fluordesoxyglucose (FDG)-avid in the PET-CT [23].

The strength of the current register-based study is the large sample size of this rare pathology to date only described in small case series. Furthermore, the data allowed for comparison of different treatment strategies. However, the study is limited by a lack of documentation of important details. No information on concomitant chemotherapy was included in SEER. However, it has to be assumed that radio-sensitising chemotherapy was part of RT and of RT/SX of patients included in SEER. Furthermore, information on the exact localization of the tumor within the rectum was not available. For the correct diagnosis of a rectal SCC, it is important to distinguish between a rectal SCC and an anal or gynecological SCC with an extension into the rectum. An anal involvement of the cancer has to be ruled out to confirm the diagnosis of a truly rectal SCC. Furthermore, the coexistence of an anal fistula to the rectum has to be ruled out and it has to be clarified that the lesion does not present a distant metastasis from other organs [12]. Given the fact that precise distinction between rectal SCC and anal SCC is difficult, the data in the registry might be ambiguous and misclassification of anal cancer cases as rectal SCC may not be excluded. Such misclassification may lead to an overestimate in survival for the group of RT as this is the usual treatment in anal cancer and survival in anal SCC is better than in rectal SCC. It was not possible to identify and eliminate potentially misclassified anal cancer cases. Nevertheless, it has to be presumed that by elimination of such cases, the survival of rectal SCC would be even worse as demonstrated. This is particularly true for the RT group.

In conclusion, in this population-based study patients with regional disease of rectal SCC undergoing multimodal therapy including surgery have an improved OS and DSS compared to those receiving a treatment without surgery. The findings contradict with recent reports favoring definitive chemoradiation as treatment of choice in rectal SCC. An orphan disease register for prospective evaluation of treatment in colorectal SCC would be desirable to obtain non-biased prospective outcome data.

Authors' contributions DCS and PCM designed the study; DCS, PCM, ATB, TB, AU, and BPM analyzed and interpreted the data; DCS and PCM drafted the article; AU, ATB, TB, and BPM performed a critical revision. All authors gave their final approval of the current version to be published. All authors agree that they are accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval For this type of study, formal consent is not required.

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